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Intervet/Schering-Plough Animal Health			HINES, JANA A	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/526,731	Applicant(s) VAN POPPEL ET AL.
	Examiner JaNa Hines	Art Unit 1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If no period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133).

Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 30 April 2008.

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 21-35 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 21-35 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO/SB/08)

Paper No(s)/Mail Date _____

4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____

5) Notice of Informal Patent Application

6) Other: _____

DETAILED ACTION

Amendment Entry

1. The amendment entered April 30, 2008 has been entered. The examiner acknowledges the amendments to the specification. Claims 1-20 and 36-38 are cancelled. Claims 33-35 have been amended. Claims 21-35 are under consideration in this office action.

Withdrawal of Rejections

2. The following objections and rejections are withdrawn in view of applicants' amendments and arguments:

- a) The objections of claims 33 and 35; and
- b) The enablement rejection of claims 34-35 under 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. The rejection of claims 21, 28-32 and 34-35 under 35 U.S.C. 102(b) as being anticipated by Wirtz et al., (1999. Molecular and Biochem. Parasit. Vol. 99: 89-101) is maintained.

The claims are drawn to an attenuated live parasite of the phylum Apicomplexa, wherein said parasite comprises a ribosomal protein gene under the control of an inducible promoter. The claims are also drawn to an immunogenic composition comprising the attenuated live parasite and a pharmaceutically acceptable carrier and a method for the production of the immunogenic composition.

The rejection was on the grounds that Wirtz et al., teach the inducible expression of transgenes including ribosomal protein genes in Trypanosome mediated by the Tet repressor (tetR) inserted in the inducible PARP promoter.

Response to Arguments

4. Applicant's arguments filed April 30, 2008 have been fully considered but they are not persuasive.

Applicants' assert that the present invention is based on the discovery that if ribosome synthesis can be stopped at or about the moment of infection, the parasite will enter the host cell and divide using the existing ribosomes and die due to the lack of ribosomes and this is achieved by placing a homologous ribosomal protein gene under the control of an inducible promoter, whereby the promoter could be deliberately switched on and off. However Wirtz et al., teach the phylum Apicomplexa, genus *Trypanosoma brucei*, wherein said parasite comprises the large subunit gene ribosomal protein gene under the control of an inducible promoter.

Applicants' urge that Wirtz et al. does not teach the regulation of rRNA genes in the original sequence in the vicinity of the inserted cassette, but the regulation of any

gene that may be inserted in their expression cassette. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies, i.e., the Wirtz et al., construct is not set up to regulate a gene of the parasite in the area of insertion is not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Therefore applicants' assertions are not persuasive, since Wirtz et al., teach the expression of a ribosomal protein, since ribosomal proteins are any of the proteins that, in conjunction with rRNA, make up the ribosomal subunits involved in the cellular process of translation.

Therefore, contrary to applicants' arguments, Wirtz et al., meets the limitations of the claims and the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. The rejection of claims 21-27 and 29-31 under 35 U.S.C. 103(a) as being unpatentable over Sutherland et al., (1996. Experimental Parasitol. Vol. 83 :125-133) in view of Xu et al., (WO 98/37185) is maintained.

The claims are drawn to an attenuated live parasite of the phylum Apicomplexa, wherein said parasite comprises a ribosomal protein gene under the control of an inducible promoter.

The rejection was on the grounds that Sutherland et al., teach the attenuation of *Theileria* cell lines and other avirulent apicomplexan protozoa and the desire and need to control gene expression in such parasites. However Sutherland et al., do not teach the parasites comprises a ribosomal protein gene under the control of an inducible promoter. Xu et al., teach the expression of genes whose products have a harmful effect and the desire and need to control gene expression in a wide variety of expression systems.

Therefore it would have been *prima facie* obvious at the time of applicants' invention to apply the attenuated live parasite of Sutherland et al., which incorporates a ribosomal protein gene under the control of an inducible promoter as taught by Xu et al., in order to provide a significant advance in the art.

Response to Arguments

6. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the

references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one of ordinary skill in the art would have a reasonable expectation of success by incorporating the ribosomal protein gene under the control of an inducible promoter as taught by Xu et al., in to the attenuated live parasite of the phylum Apicomplexa as taught by Sutherland et al., because Xu et al., teach that an inducible system advantageously provides stringent regulation of gene expression in prokaryotes, thereby requiring the use of smaller amounts of tetracycline in order to function effectively. Therefore contrary to applicants' assertions that there is no suggestion of controlling ribosomal protein expression in a parasite, no more than routine skill would have been required to incorporate the ribosomal protein gene under the control of an inducible promoter since Xu et al., teach the expression of genes whose products have a harmful effect and the need to control gene expression in a wide variety of expression systems by incorporating a ribosomal protein gene under the control of an inducible promoter to advantageously achieve a less toxic live attenuated prokaryotic cell line.

Therefore applicants' arguments are not persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The rejection of claims 21, 28-32 and 34-35 under 35 U.S.C. 103(a) as being unpatentable over Titus et al., (1995. PNAS, Microbio. Vol. 92:10267-10271) in view of Yan et al., (2001. Mol. & Biochem. Parasitol. Vol.112 :61-69) is maintained.

The claims are drawn to an attenuated live parasite of the phylum Apicomplexa, wherein said parasite comprises a ribosomal protein gene under the control of an inducible promoter. The claims are also drawn to an immunogenic composition comprising the attenuated live parasite and a pharmaceutically acceptable carrier and a method for the production of the immunogenic composition.

The rejection is on the grounds that Titus et al., teach the development of a safe live attenuated *Leishmania* vaccine by gene replacement; however Titus et al., do not teach *Leishmania* comprising a ribosomal protein gene under the control of an inducible promoter. Yan et al., teach tetracycline regulated gene expression in *Leishmania* with an inducible system that provides stringent regulation of gene expression in *Leishmania* while offering great advantages.

Therefore it would have been *prima facie* obvious at the time of applicants' invention to apply the attenuated live parasite of Titus et al., which incorporates a ribosomal protein gene under the control of an inducible promoter as taught by Yan et al., in order to provide more effective protective *Leishmania* vaccines.

Response to Arguments

8. Applicant's arguments have been fully considered but they are not persuasive.

Applicants assert that the art does not describe the ribosomal genes as targets for disruption or regulation. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies, i.e., that the ribosomal genes as targets for disruption or regulation are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Therefore applicants' argument is not persuasive, since the art does teach an attenuated live parasite of the phylum Apicomplexa, wherein said parasite comprises a ribosomal protein gene under the control of an inducible promoter.

Applicants' argue that the combination of Titus et al. and Yan et al. would not suggest to the ordinary practitioner to obtain an attenuated live parasite by controlling its ribosomal protein gene using an inducible promoter. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*. In this case, no more than routine skill would have been required to incorporate the ribosomal protein gene under the control of an inducible promoter since Yan et al.,

teach that conventional gene replacements strategies are unlikely to be useful in the production of stable live attenuated cell lines. Furthermore, it would have been *prima facie* obvious to combine the invention of Titus et al., and Yan et al., to have an attenuated live parasite of the phylum Apicomplexa, wherein said parasite comprises a ribosomal protein gene under the control of an inducible promoter and advantageously achieve less toxic protective vaccines that manage *Leishmania* infections.

Therefore, applicants' arguments are not persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 33 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 33, the term "preferably" renders the claim indefinite because it is unclear whether the limitation(s) following the term is part of the claimed invention. The term "preferably" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Thus the metes of bounds of the claim are unclear and clarification is required to overcome the rejection.

Conclusion

10. No claims allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Shanon Foley, can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/
Primary Examiner, Art Unit 1645